PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE2004/000134	22.09.2004	22.09.2003

International Patent Classification (IPC) or both national classification and IPC
C07D213/80, C07D213/69, A61K31/4412, A61P31/18

Applicant
FACULTES UNIVERSITAIRES NOTRE-DAME DE LA PAIX

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Usuelli, A

Telephone No. +49 89 2399-7366

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/BE2004/000134

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/BE2004/000134

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☒ complied with

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,17
	No:	Claims	14-16
Inventive step (IS)	Yes:	Claims	2-4,17
	No:	Claims	1,5-16
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/BE2004/000134

Re Item IV

Lack of unity of invention

Present application relates to the compounds of formula (I) having anti-HIV inhibiting properties (claims 1 to 13 and 17), to a method for obtaining irreversible anti-HIV-1 compounds (claims 14,15) and to the compounds obtained by this method (claims 16 and 17). The method according to claims 14 and 15 is not limited to the obtention of anti-HIV compounds having a defined chemical formula. In particular said method is not limited to the obtention of the compounds according to claim 1.

When an application relates to a group of inventions the requirements of unity are fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are those features which define a contribution over the prior art (Rule 13.2 PCT). In the present case, the sole relationship among the claims relating to the compounds of formula (I) and the claims 14 to 16 is the fact that they all relate to the inhibition of HIV. However, the presence of unity cannot be based upon this generic relationship since compounds inhibiting the HIV are already part of the state of the art. In other words the relationship between the claims relating to the compounds of formula (I) and the claims 14 to 16 is not based upon any special technical features in the sense of Rule 13.2 PCT .

For these reasons it is considered that the subject matter concerning the compounds of formula (I) (claims 1-13 and 17) and the subject matter relating to the process of claim 14 (claims 14-17) are not linked as to form a single inventive concept (Rule 13.1 PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents cited in the search report:

d1: WO 99/55676 A

d2: WO 02/24650 A

d3: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 23, 15 October 1995 (1995-10-15), pages 4679-4686

d4: WO 98/37072 A

d5: BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, no. 2, 23 January 1996 (1996-01-23), pages 173-178

2- Novelty - **Claims 1-13 and 17**

Present compounds of formula (I) differ from the compounds disclosed in d1 to d5 mainly on account of the group X-R2.

Hence, the requirements of Art. 33.2 PCT are met.

3- Inventive activity - **Claims 1-13 and 17**

3.1- The applicant has set himself the task of providing novel HIV-1 inhibitors to be used in the treatment of AIDS.

Documents d1 to d5 relate to pyridone derivatives having the same therapeutic applications of the present compounds.

Taking into account of the compounds disclosed in these three documents, it appears that the closest prior art is represented by d2.

3.2- The results disclosed in Tables 3 to 8 provide the evidence that present compounds wherein R2 contain a non-aromatic cyclic moiety (see definition of R2 on page 32) indeed solve the technical problem of providing novel anti HIV agents.

None of the prior art documents suggests the preparation of pyridone derivatives characterised by the presence of a non-aromatic cyclic group in position 4. Thus, these compounds appear to comply with the requirements of Art. 33.3 PCT (claims 2-4,17).

3.3- The description does not provide any data concerning the biological activity of present compounds of formula (I) wherein R2 is an aromatic group (R2= COAr(CH2)nW - page 33).

However, since d1 to d3 disclose various HIV-1 inhibitors having similar groups in the same position, it appears reasonable to assume that also these compounds have the desired activity.

For the same reasons it appears that these compounds are obvious in the light of d1 to d3. For instance, the compounds 69 and 158 of d2 seem to differ from present compounds mainly on account of the linking group between the pyridone and the aromatic ring (in this context is observed that present group R1 may also be a hydrogen or a dimethylamino group when R1=(CH2)nY and n=0, Y=H or N(CH3)2).

However, taking into account of the definitions of the groups X in d1 and d2 (i.e. "the linking moieties") the skilled person would deduce that various binding moieties may be present as linkers between the pyridone and the aryl or heteroaryl groups.
In general, considering the compounds disclosed in d1 to d3, it appears that the skilled person faced with the problem of providing novel HIV inhibitors, would consider obvious to prepare pyridone derivatives having a group containing an aromatic ring in position 4.
Accordingly, the subject matter of claims 1 and 8 to 13 does not meet the requirements of Art. 123.2 PCT.

3.4- The compound M18 is the sole compound tested wherein R2 is a moiety which does not contain any cyclic group.
The experimental data concerning this compound, clearly indicate that M18 is substantially less active and more cytotoxic than the other compounds. These results may cast some doubt about the possibility of using present compounds wherein R2 does not contain a cyclic group (i.e. R2= COCH=C(CnH2n+1)2; -(CH2)n-CO(CH2)mW as HIV inhibitors.
Thus, at present it is not evident whether these compounds represent a solution of the technical problem.
It is pointed out that in the absence of an activity convincingly shown, the technical problem solved would be considered the mere provision of further chemical compounds. However, such a problem is not acceptable because a chemical compound is not considered patentable merely because it potentially enriches the chemistry.
Accordingly, the compounds wherein R2 is a moiety which does not contain any cyclic group (claims 5-7) are not inventive because they don't solve any acceptable technical problem.

4- Novelty - **Claims 14-16**
Claim 14 and 15 relate to a method for preparing irreversible anti-HIV-1 compounds which are capable to covalently bind an amino acid of an HIV-1 enzyme. The method essentially consists in selecting an anti-HIV-1 compound and in introducing a chemical modification in its structure.
Both the description and the claim fail to provide specific instructions about to technical measures to be adopted in order to obtain a compound having the desired properties, i.e. a compound which is an irreversible anti-HIV-1 compound and is capable to bind covalently an amino acid of an HIV-1 enzyme. In particular, it is not explained how the

starting anti-HIV-1 should be selected and which chemical modifications should be carried out.
In the absence of this technical information, claims 14 and 15 are regarded as a method for preparing an anti-HIV compound by chemical modification of another anti-HIV compound.
However, such a method for preparing an anti-HIV compound is already state of the art in view of the following disclosures:
- d3 discloses in scheme 4 the preparation of the anti HIV compound of formula 17 by chemical modification of the anti-HIV compound of formula 16.

- d5 discloses in scheme 2 the preparation of the anti HIV compound of formula 14 by chemical modification of the anti-HIV compound of formula 13.

Hence, claims 14 to 15 lack of novelty. As consequence, also claim 16 which concerns compounds obtainable by the processes of claims 14 and 15 is not novel.
Having regard to claim 16, it is observed that the wording "obtainable by said method", cannot be regarded as a limiting feature since said wording does not allow to define any property, including the structure, of the compounds claimed. Hence, claim 16 merely relate to an irreversible NNRTI. Hence, claim 16 lacks of novelty also vis-à-vis d4 which discloses irreversible non-nucleoside reverse transcriptase inhibitors (cf. first paragraph of page 8).